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The Molecular Basis of Chemical Toxicity

by James D. McKinney*

Studies of structure–activity relationships and molecular mechanisms of action are fundamental to our understanding of the harmful effects of chemicals on the environment and their more direct effects on human health. It is important to identify factors that determine toxicological effects of foreign chemicals in biological systems and to assess our knowledge about chemical mechanisms of toxicity. Several fundamental mechanisms underlying toxic action are described, and the importance of studying receptor–substrate interactions is stressed. The *Ah* receptor is cited as an example of a protein–small molecule interaction associated with extreme acute toxicity in laboratory animals. It is recognized that reliable attempts at predictive toxicology across compound classes through structural and theoretical chemistry approaches must be based on sound knowledge about mechanisms of action at the molecular level. Such studies also contribute to the knowledge base in biomedical and physical sciences.

Introduction

An area of toxicology research that is increasing in importance is concerned with elucidating the mechanisms by which chemicals exert their toxic action on living organisms. The study of mechanisms of toxic action is not new and can be traced back to as early as 1809 with the study of the mechanisms of action of arrow poisons, such as strychnine (*1*). Increasing attention to this area of research stems from the fact that such studies often lead to sensitive predictive tests useful in obtaining information for risk assessment, helping develop chemicals that are safer, or suggesting rational therapy for toxic symptoms. In addition, an understanding of molecular mechanisms of toxic action contributes to the knowledge base in biomedical and physical sciences. Thus, the elucidation of molecular mechanisms of action can, in the long run, be the most cost-effective approach for studying problems related to environmental health diseases. We recognize that in the practical sense the critical factor is not the intrinsic toxicity of a substance *per se* but the risk or hazard associated with its use. It is clearly important to consider harmful effects on the environment as well as more direct effects on human health. Fundamental studies of structure–activity relationships and molecular mechanisms of action also contribute to our understanding in these areas as well.

A great deal of effort has already been devoted to elucidating biochemical mechanisms of toxicity, and there is a growing body of literature which reflects this (*1*). However, mechanism of action means different things to different people, and in this work the emphasis will be on the actual understanding of events leading to a toxic response at the level of molecular interactions and reactions. There is considerably less known about mechanisms of toxicity at the truly molecular level. The investigator who proposes a molecular mechanism of action almost always extends himself beyond the data available to make the claim. However, mechanistic hypotheses are an important part of the research in this area and provide sense of direction by suggesting further experimentation to test the proposed mechanism. Such additional experimental work may involve approaches not readily available to the investigator making the initial mechanistic claim. In addition, knowledge about the molecular mechanism should enable one to design test molecules that contain the required molecular determinants of activity in structurally similar and dissimilar classes of compounds.

Research Approaches to Studying Molecular Mechanisms Underlying Toxic Action

The purpose of this paper is not to review the large body of literature on mechanisms of toxicity but to emphasize the fundamental importance of structure–activity, molecular and theoretical modeling approaches to studying molecular mechanisms of action and predictive toxicology (*2–11*). In doing this, we will attempt to identify factors which determine toxicological effects of foreign chemicals in biological systems, to assess our knowledge about chemical mechanisms of toxicity, to

*Laboratory of Molecular Biophysics, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709.

outline several fundamental mechanisms, and to stress, by using a specific example, the importance of studying receptor–substrate interactions and vectorial chemistry (reactions that seem to depend on concentration gradients for their driving force such as those important in transport of molecules across membranes).

It is certain that the biological activity of a compound resides somewhere in the chemical makeup of the molecule. Some of the factors which determine toxicological effects of foreign chemicals in biological systems are: (1) molecular features related to size, shape, symmetry, and associated substructural features; (2) electronic structural features acting separately or in combination; (3) physicochemical properties, especially as they relate to lipophilicity and ability to reach the site of action; (4) interference with normal processes and function at the molecular level (mechanism of action). The first two factors listed describe a range of structural and physical–chemical properties which determine the actual interactions and reactions of a given chemical in any matrix. The associated physicochemical properties are especially important in determining the kinetic factors which relate to lipophilicity and ability of the compound to reach the site of action. These factors include absorption, distribution, metabolism and excretion. At the site of action the compound can interfere with normal processes and function at the molecular level and such effects are almost always mediated by selective interaction with one or more proteins. Biological systems are not without biochemical defense mechanisms such as detoxification and repair processes which can often modulate the toxic response.

In assessing our knowledge about chemical mechanisms of toxicity, it is convenient to list the important interrelated factors (as done for two cases in Table 1) that define a toxic response at the molecular level. The more detailed and specific the information is, the more likely the molecular mechanism of action can be understood. For example, there is an increasing body of evidence (*12*) that the carcinogenic action of certain halogenated and nonhalogenated hydrocarbons is due to metabolic activation and generation of reactive electrophilic species which undergo covalent binding to biological macromolecules ultimately leading to cancer. However, this can be viewed as occurring in several sequential steps which may be dependent on the same or different structural properties for effective interaction or reaction. The compound presumably binds to transport proteins that carry it to the site(s) of action where it binds to other proteins in cells (such as cytosol protein) and undergoes metabolic activation either before or after translocation to the nucleus. The reactive metabolites can then undergo covalent binding to macromolecules either nonenzymatically or through further metabolic transformation. Finally, not all covalent binding adducts will lead to carcinogenic endpoints because of biological repair processes. Therefore, it is apparent that a complete understanding of the molecular mechanism of even one specific carcinogen of this type will be difficult and involve the study of many processes and interactions singly and in combination.

In contrast, the study of the mechanism of toxicity of dioxin and related compounds has suggested that specific protein receptor interactions are involved, but there is little evidence to support metabolic activation and covalent binding to macromolecules. In fact, after considerable research study (*13*), the biochemical leison(s) resulting in toxicity is not known although a number of factors have presumably been ruled out.

In Table 1, the first two categories and the last category listed deal with the biomolecular interactions (for example, initiating event) involved and the toxic endpoints while the remaining categories deal with specific structural information important in the toxicity (for example, toxicophore). Approaches to studying chemical mechanisms of toxicity can take the form of developing prototype compounds that enable detailed study of specific biochemical and molecular events. Alternatively, one can investigate the effects of structural modifications on the toxic outcome both qualitatively and quantitatively to learn what one can about the nature of the molecular interactions and reactions the chemicals may prefer to undergo in a given biological system. In either of these approaches, it is clear that methods are needed to accurately assess both structure and molecular reactivity properties as well as biological activities and responses in a given system. Our ability to assess relevant structure and molecular reactivity properties can be both experimental and theoretical while our ability to assess biological activities and responses still remains

Table 1. Assessing knowledge about chemical mechanisms of toxicity—chemical carcinogenicity and acute toxicity.

Signs and symptoms	Initiating event	Chemical name	Chemical classes	Substructure analysis	Toxicophore	Biochemical leison
Tumor formation, cancer	Protein interaction and metabolic activation	Benzo(a)pyrene Chloroform Vinyl chloride	Aromatic hydrocarbons Halogenated hydrocarbons	Arene oxides Electron deficient carbon Epoxides	Electrophiles (covalent binding to macromolecules)	Binding to nucleic acids(?)
Debilatation of lymphatic system, thymic involution, wasting syndrome, lethality	*Specific bio-*receptor interaction(?)	*Halogenated* Dioxins Furans Naphthalenes Biphenyls	*Halogenated* aromatic hydrocarbons	*Number and* position of halogens Planarity Size and shape of molecule	*Polarizability* properties (non-covalent binding)	*Not known*

largely experimental. However, through the development of linear free energy and quantitative structure–activity relationships, we should be able to increase our understanding of biomechanisms and successful prediction of their associated activities and responses.

Some Fundamental Molecular Mechanisms Underlying Toxic Action

Four relatively common and perhaps widely accepted mechanisms underlying toxic action are described to illustrate the diversity and multidisciplinary nature of the research problems involved. The toxicity of chemicals is often limited to one or more specific target organs. Localization of a chemical in a specific target organ may be a function of kinetic factors such as an active transport system. The bipyridylium herbicide, paraquat, is highly toxic to the lung following systemic absorption (*14*), and this is related to the ability of the lung to accumulate paraquat via an active transport system specific for several amines (*15*). The structurally related compound diquat is much less toxic to the lung because it is not a substrate for the transport system. Thus, while both of these compounds may have similar molecular mechanisms of toxicity if studied at the cellular or subcellular level in the lung, only one is relatively toxic if studied in a whole animal model. Stated another way, structural requirements important in determining kinetic factors may or may not be important in determining the molecular events at the site of action. This example emphasizes the importance of doing a complement of *in vitro* and *in vivo* studies in elucidating molecular mechanisms of toxic action important in health hazard assessment. This example further emphasizes the role of structure–pharmacokinetic relationships in predictive toxicology.

The toxicity of other chemicals can be the result of relatively specific interference with a critical metabolic process. Often chemicals in this category will function as antimetabolites and/or suicide substrates for normal endogeneous substrates of specific proteins or enzymes. Paraoxon, an activated metabolite of the organophosphate pesticide parathion, appears to function as a suicide substrate for acetyl cholinesterase by selectively phosphorylating the esteratic site of this enzyme (*16*). The toxicity associated with these compounds is characterized by a disruption of the nervous system function due to accumulation of acetylcholine in the nerve synapses. Atropine has been used to treat organophosphate poisoning by blocking acetycholine build-up. Compounds that produce toxicity by this type of mechanism appear to bear close structural similarity to normal substrates of important metabolic processes. Therefore, it is of obvious importance to delineate, on a structural basis, such small molecule–protein interactions involved in normal biological processes.

Metabolism is important in both the bioactivation and detoxification of a wide variety of xenobiotic compounds. Metabolic activation appears to be a process by which many chemicals can undergo transformation usually to electrophilic species that are capable of covalent binding to cellular macromolecules, in some cases without further enzymatic assistance. Reactive metabolites of this type include epoxides (*17*), arene oxides (*12*), diolepoxides, semiquinone radicals (*18*), anion or cation radicals (*19*), activated conjugates (*12*), etc. The potential toxic reactions of many of these reactive intermediates are controlled by several important enzymatic and nonenzymatic detoxification mechanisms. The products of such detoxification reactions are generally less toxic and more readily excreted. An extensively studied class of agents whose toxicity is mediated by formation of reactive arene oxide and epoxides is the polycyclic aromatic hydrocarbons (PAHs) as represented by beno(a)pyrene. Stereochemical factors appear to play an important role in the metabolic activation of PAHs, and these factors may have predictable outcomes (*20*).

Compounds that are metabolically activated in this way often possess electron-rich centers for initial attack by electron deficient oxygen species associated with the mixed-function oxidases. Because of the diversity of electrophilic species that can be generated upon activation, several toxic endpoints are seen, sometimes in many organ systems, including general toxicity and necrosis, carcinogenicity and mutagenicity. It is important to note that the end result of tissue interaction with these activated species is alteration of the structural integrity of biological macromolecules in a way that their function in normal cellular processes is impaired or prevented. Since the macromolecules involved have undergone covalent modification of their structure, one might also expect normal degradative and repair processes to be less effective.

As illustrated in these representative biomechanisms, it is important to recognize that essentially all biological processes are mediated by the selective interaction of a protein receptor with one or more specific substrates. To study these processes in molecular detail for understanding mechanisms of biological action, it is important to identify the active structures in electronic and stereochemical terms of endogenous substrates and substrate analogs, to understand what structural features are required for activity as well as those which can modulate the activity, and to anlayze their interaction with the receptors in physical–chemical and biological terms.

Interest in the structural basis for action of proteins dates back to 1894, when Emil Fisher (*21*) introduced the idea that an enzyme and its substrate have a "lock and key" type structural complementarity. However, even now, more than 20 years after the beginning of X-ray structural revolution in biochemical studies, we still do not have a unique explanation for the relationship of protein structure and specific biological responses. Several lines of research (*22–24*) are, however, supporting a dynamic description of protein action with demon-

strated conformational fluctuation and flexibility. This flexibility is believed necessary for the explanation of many important physiological effects controlled by protein and enzyme action. Studies (*25*) point toward electrostatic interactions as the common denominator and probably the most important element in structure–function correlation in biological systems. Steric complementary alone does not seem to be a major factor, although it has obvious importance in determining a unique electrostatic condition.

As expected, there is increasing evidence that toxicity is also mediated by protein–receptor interactions. A protein receptor involvement that is receiving considerable attention at the moment is the extreme acute toxicity of the halogenated dioxins and related compounds which is believed to be mediated by a cytosolic protein referred to as the dioxin or *Ah* receptor (*13*). This is supported by two independent lines of evidence: the correlation of the structure–activity relationship for receptor binding and that for toxic potency; and segregation of three toxic responses produced by TCDD in the mouse with the *Ah* locus. It has been proposed that a rectangle 3 × 10 Å with halogens in the four corners serves as a rough approximation for the generalized structure–activity relationship involving these receptors. However, it is clear that such a model does not have universal applicability. For example, this model does not account for the nonhalogenated polycyclic aromatic hydrocarbons and benzoflavones, which bind to the *Ah* receptor, some with near equal affinities to the halogenated aromatic hydrocarbons. Therefore, there is clearly a need for more detailed molecular study of this important protein receptor interaction with such highly toxic molecules. It is important to note that the parent compounds—and not metabolites—are responsible for the toxicity of these compounds (*13*), which differs fundamentally from the protein interactions discussed previously which involves the breaking and formation of covalent bonds in their molecular mechanism of action.

Recent Studies on the Molecular Nature of *Ah* Receptor Interactions

We seek a molecular interpretation of the relationship between cytosolic protein receptor binding affinities and the molecular structure of the halogenated aromatic hydrocarbons and related compounds. Binding studies (*26*) with representative halogenated and nonhalogenated compounds lead one to conclude that binding to the *Ah* receptor is facilitated by an aromatic ring system for which molecular size, halogen substitution and coplanarity of rings are not critical but may affect the strength of binding. This suggests a stacking type (dispersion interaction) model for the molecular complexes which has been supported experimentally (*26*) through the demonstration of charge–transfer type complexes between 3-methylindole acting as an electron donor and certain aromatic compounds acting as electron acceptors. Further support for the stacking type interaction has come from the development of a theoretical model and quantitative structure–activity relationship (*27*) based on dispersion interactions between the cytosol binding proteins and polychlorinated biphenyls (PCBs). The essential parameters in the model are the PCB polarizability and the receptor to PCB separation distance determined by stereochemical factors. A model also suggested that there is a hydrogen bonding component of the receptor which may reasonably account for the unusual binding affinity of certain dioxins. Previous theoretical findings of other workers (*28*) have also suggested the importance of an effective donor–acceptor type interaction for *Ah* receptor binding.

Therefore, in considering possibilities for endogenous substrates for the *Ah* receptor, it is important to think in terms of aromatic compounds which can function as electron acceptors in stacking interactions and perhaps can undergo hydrogen bonding. The thyroid hormones clearly stand out among the possible choices as substrates for these receptor proteins. [The possible potent electron accepting ability of the thyroid hormones has been previously discussed (*29*).] Using a new assay procedure (*30*) for these receptors which shows less nonspecific binding than previous assays, we estimated the binding affinities of the thyroid hormones (T_3 and T_4) to the *Ah* receptor. Table 2 demonstrates that thyroid hormones can interact with the *Ah* receptor. T_3 was seen to bind the cytosol receptors with about 1/10 the affinity of dioxin (TCDD), while the affinity of T_4 was less than that of T_3. This ability to interact with the *Ah* receptor is further supported by the demonstration that both T_3 and T_4 can potentiate the teratogenicity of TCDD, a toxic effect believed to involve the *Ah* receptor. T_4 is about an order of magnitude less effective than is T_3 (*31*).

TCDD has been shown (*32*) to bind the *Ah* receptor with equilibrium dissociation constants in the 10^{-9} to 10^{-8} range. The results given in Table 2 are consistent with the known affinities ($K_d \approx 10^{-7}$) of the thyroid hormones for some cytosol proteins (*33*) and the some-

Table 2. Competition with ^{125}I-dioxin binding to cytosol receptors.

Ligand	Relative inhibition, %[a]		
	10^{-5} M	10^{-6} M	10^{-7} M
TCDD	ND[b]	100	86
3,3′,5-Triiodothyronine (T_3)	94	27	0
3,3′,5,5′-Thyroxine (T_4)	47	0	0
2,4,6-Triiodophenol (TIP)	—	92	35

[a] Since the specific activity of the labeled ^{125}I-dioxin was not known, it was not possible to obtain equilibrium binding constant data. However, relative binding data was obtained by determining the competitive binding by test compounds at different concentrations as compared to 10^{-6} M unlabeled TCDD (set equal to 100). ^{125}I-dioxin = [^{125}I] iodovaleramide derivative of trichlorodibenzo-*p*-dioxin.

[b] ND = not done.

what lower affinity of T_4. The lower affinity of T_4 relative to T_3 is believed to be associated with the possible steric influence of iodine on T_4 hydrogen bonding interactions (*34*). As previously described (*27*), a hydrogen-bonding component of the *Ah* receptor may account for the unusual binding affinity of certain dioxins. The failure of other workers (*32*) to demonstrate thyroid hormone binding to the *Ah* receptor may be a reflection of the high level of nonspecific binding in their assays and the fact that they apparently tested only T_4 which has significantly less binding affinity than T_3.

It is also reasonable to propose that stacking interactions involving an aromatic ring of the thyroid hormones can occur since their crystallographically determined structures (*35*) indicate that the two phenyl rings linked by a C–O–C angle of 120° are disposed nearly perpendicular and bisecting, which provides the molecular flexibility needed. Removal of the ether oxygen to form the linear biphenyl analogs, which because of *ortho* iodination would have weak stacking interactions (*27*) but otherwise possess structural features that impart strong dispersion interactions, results in apparent loss of thyroid hormone activity in limited tests (*36*). This supports a stacking-type complex as a part of the mechanism of thyroid hormone action. This argument is further supported by the efficient binding of the single ring triiodophenol compound shown in Table 2, which lacks any steric hindrance to stacking interactions. Such stacking or dispersion type interactions would be consistent with charge transfer complexation. Charge transfer complexation is one description (*37*) of the molecular nature of a protein recognition site that could lead to an activated complex and a subsequent biological response.

It is interesting to speculate that the dioxin or *Ah* receptor may be among the cytosol proteins for thyroid hormones responsible for their translocation to the nucleus, their likely site of action. Unsuccessful attempts to demonstrate a cytosol protein–thyroid hormone receptor complex translocation (*33*) may reflect the relatively low binding affinity of T_3 and T_4 for the cytosol receptors. Since TCDD binds the receptor with an affinity several orders of magnitude higher, it may have been easier to demonstrate such a translocation. Consistent with the hypothesis that these cytosol receptors may function as storage and translocating proteins for thyroid hormones is the finding (*33*) that T_3 binds to nuclear binding sites with markedly higher affinity than the cytosol sites whereas the cytosol has greater capacity for T_3. This may be an example of vectorial chemistry in which the resulting concentration gradient apparently controls occupancy of the nuclear sites that may be needed for normal function. In this regard, recent work (*38*) has shown that aqueous dilution during subcellular fractionation of mouse hepatoma cells influences the distribution of *Ah* receptors between the nuclear and cytosolic fractions. A temperature-dependent event was also shown to enhance the binding of TCDD-receptor complexes to nuclei. Similarly, T_3, but not T_4, binding activity to solubilized nuclear receptors has been shown (*39*) to be dilution, temperature, and pH dependent.

Nevertheless, these recent studies of the *Ah* receptor interaction are suggesting a different molecular interpretation of the relationship between receptor binding and molecular structure. It is clear (*27*) that the *Ah* receptor is better represented by a model based on molecular polarizability and equilibrium separation between the receptor and effector molecule. These molecular parameters define a more universally applicable model since this model can explain the exceptions found for the previously proposed box model (*13*). The accumulating evidence that the *Ah* receptor has properties in common with a thyroid hormone receptor is also of considerable interest, not only with regard to the mechanism of dioxin toxicity but also with regard to the molecular mechanism of thyroid hormone action.

Conclusion

It is apparent that a complete understanding of the molecular mechanisms of toxic action will be a difficult and slow process involving the study of many molecular interactions and reactions singly and in combination. The molecular mechanism of action of chemicals may vary even among compounds of the same chemical class for reasons that are not always obvious. Thus, the development of structure–activity relationships for predictive purposes must be done with extreme care and always checked with test compounds not in the training set. Where possible QSAR work should be done in association with molecular mechanism work for mutual guidance and direction. Knowledge about molecular mechanisms is the best approach to designing test molecules that contain the required molecular determinants of activity in structurally similar and dissimilar classes of compounds. In addition, knowledge about mechanisms is perhaps the only hope for suggesting rational therapy for toxic symptoms of compounds already in our environment.

As suggested by the work on the molecular nature of *Ah* receptor interactions, a molecular understanding of undesirable biological interactions may provide further insight into fundamental biological processes and molecular mechanisms of action for endogenous substrates. Thus, the elucidation of molecular mechanisms of action can in the long run be the most cost effective approach for studying problems related to human health diseases. The study of biorecepter interactions is also gaining in importance and recognition through the application of molecular modeling techniques combined with interactive computer graphics.

Thus more research effort needs to be devoted to studying molecular mechanisms underlying toxic action to enable the toxicologist to better extrapolate from general mechanisms to defining the potential toxicity of

specific chemicals. In addition, such work can help in the health hazard assessment area by identifying compounds on which to focus our analytical and toxicological attention. Furthermore, any reliable attempts at predictive toxicology across compound classes through structural and theoretical approaches must be based on sound knowledge about mechanisms of action at the molecular level.

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REFERENCES

1. Doull, J., Klaassen, C. D., and Amdur, M. O. Casarett and Doull's Toxicology. Macmillan Publishing Co., New York, 1980.
2. Sexton, W. A. Chemical Constitution and Biological Activity. D. Van Nostrand Co., New York, 1953.
3. Korolkovas, A. Essentials of Molecular Pharmacology. Wiley-Interscience, New York, 1970.
4. Gould, R. F. (Ed.). Biological Correlations—The Hansch Approach (Advances in Chemistry Series, Vol. 114). American Chemical Society, Washington, DC, 1972.
5. Cavallito, C. J. (Ed.). Structure–Activity Relationships, Vol. I. International Encyclopedia of Pharmacology and Therapeutics, Pergamon Press, New York, 1973.
6. Arcos, J. C., and Argus, M. F. Chemical Induction of Cancer. Structural Bases and Biological Mechanisms, Vols. I–III. Academic Press, New York, 1974.
7. Asher, I. M., and Zervos, C. Structural Correlates of Carcinogenesis and Mutagenesis. A Guide to Testing Priorities? Proceedings of the Second FDA Office of Science Summer Symposium, Office of Science, FDA, HEW Publication No. (FDA) 78–1046.
8. Walters, D. B. (Ed.). Safe Handling of Chemical Carcinogens, Mutagens, Teratogens and Highly Toxic Substances, Vol. 2, Section IV. Ann Arbor Science, Ann Arbor, MI, 1980.
9. Bhatnagar, R. S. (Ed.). Molecular Basis of Environmental Toxicity. Ann Arbor Science, Ann Arbor, MI 1981.
10. McKinney, J. D. (Ed.). Environmental Health Chemistry. Ann Arbor Science, Ann Arbor, MI, 1981.
11. Goldberg, L. (Ed.). Structure–Activity Correlation as a Predictive Tool in Toxicology—Fundamentals, Methods, and Application. Hemisphere Publishing Corp., Washington, DC, 1983.
12. Weisburger, E. K. Metabolism and activation of chemical carcinogens. Mol. Cell. Biochem. 32: 95–104 (1980).
13. Poland, A., and Knutson, J. C. 2,3,7,8–Tetrachlorodibenzo-*p*-dioxin and related compounds. Examination of the mechanism of toxicity. Ann. Rev. Pharmacol. 22: 517–554 (1982).
14. Heath, D., and Smith, P. The pathology of the lung in paraquat poisoning. In: Biochemical Mechanisms of Paraquat Toxicity (A. P. Autor, Ed.), Academic Press, New York, 1977, pp. 39–51.
15. Rose, N. S., and Smith, L. L. The relevance of paraquat accumulation by tissues. In: Biochemical Mechanisms of Paraquat Toxicity (A. P. Autor, Ed.), Academic Press, New York, 1977, pp. 71–91.
16. Main, A. R. Cholinesterase inhibitors. In: Introduction to Biochemical Toxicology (E. Hodgson and F. E. Guthrie, Eds.), Elsevier, New York, 1980, pp. 193–223.
17. Manson, M. M. Epoxides — is there a health hazard? Brit. J. Ind. Med. 37: 317–336 (1980).
18. DeVries, J. Heptatoxic metabolic activation of paracetamol and its derivatives phenacetin and benorilate: oxygenation of electron transfer. Biochem. Pharmacol. 30: 399–402 (1981).
19. Haber, F., and Weiss, J. The catalytic decomposition of hydrogen peroxide by iron salts. Proc. Roy. Soc. (London) A147: 332–351 (1934).
20. Guengerich, F. P., Fu, P. P., MacDonald, T. L., Kaminsky, L., and Adams, S. M. Applications of theoretical chemistry in the prediction of metabolism. Trends Pharmaceut. Sci. 4: 443–446 (1983).
21. Fisher, E. Einfluss der Konfiguration auf die Wirkung der Enzyme. Ber. Dtsch. Chem. Ges. 27: 2985 (1894).
22. Weber, G. Ligand binding and internal equilibria in protein. Biochem. 11: 864–878 (1972).
23. Leonard, N. J. Dimensional probes of enzyme–coenzyme binding sites. Accts. Chem. Res. 15: 128–135 (1982).
24. Lipscomb, W. N. Acceleration of reactions by enzymes. Accts. Chem. Res. 15: 232–238 (1982).
25. Warshel, A. Electrostatic basis of structure–function correlation in proteins. Accts. Chem. Res. 14: 284–290 (1981).
26. McKinney, J. P., Chae, K., McConnell, E. E., and Birnbaum, L. Structure-induction versus structure–toxicity relationships for polychlorinated biphenyls and related aromatic hydrocarbons. Environ. Health Perspectives 60: 57–68 (1985).
27. McKinney, J. D., Long, G. A., and Pedersen, L. PCB and dioxin binding to cytosol receptors. A theoretical model based on molecular parameters. In: QSAR Pharmacol. Chem. Biol. 3: 99–105 (1984).
28. Cheney, B. V., and Tolly, T. Electronic factors affecting receptor binding of dibenzo–*p*–dioxins and dibenzofurans. Int. J. Quantum Chem. 16: 87–110 (1979).
29. Lovelock, J. E. Affinity of organic compounds for free electrons with thermal energy: its possible significance in biology. Nature 189(4765): 729–732 (1961).
30. Chae, K., Albro, P. W., Luster, M. I., and McKinney, J. D. A screening assay for the tetrachlorodibenzo-*p*-dioxin receptor using the [^{125}I]–iodovaleramide derivative of trichlorodibenzo-*p*-dioxin as the binding ligand. Internatl. J. Environ. Anal. Chem. 17: 267–274 (1984).
31. Lamb, J. C., Harris, M. W., Weber, H., McKinney, J. D., and Birnbaum, L. Potentiation of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) induced cleft palate (CP) by triiodothyronine (T_3) in C57BL/6N (B6) mice. Biol. Reprod., in press.
32. Poland, A., and Glover, E. Stereospecific high affinity binding of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin by hepatic cytosol. J. Biol. Chem. 251: 4936–4946 (1976).
33. Dillman, W., Surks, M. I., and Oppenheimer, J. H. Quantitative aspects of iodothyronine binding by cytosol proteins of rat liver and kidney. Endocrinology 95: 492–498 (1974).
34. Andrea, T. A., Dietrich, S. W., Murray, W. J., Kollman, P. A., and Jorgensen, E. C. A model for thyroid hormone–receptor interaction. J. Med. Chem. 22: 221–232 (1979).
35. Cody, V. Thyroid hormone interactions: molecular conformation, protein binding, and hormone action. Endocrine Rev. 1(2): 140–166 (1980).
36. Li, Choh Hao (Ed.). Hormonal Proteins and Peptides. Vol. VI, Academic Press, New York, 1978, Chapt. 2.
37. Mauchamp, J., and Shinitzky, M. The nature of thyroxine and related compounds as electron donors. Biochemistry 8: 1554–1557 (1969).
38. Whitlock, J. P., and Galeazzi, D. R. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin receptors in wild type and variant mouse hepatoma cells. J. Biol. Chem. 259: 980–985 (1984).
39. Eberhardt, N., Ring, J. C., Latham, K. R., and Baxter, J. D. Thyroid hormone receptors. J. Biol. Chem. 254: 8534–8539 (1979).